Remarks/Arguments:

Claims 9-19, presented hereby, are pending.

Claims 1-8 are cancelled hereby, without prejudice or disclaimer.

Present claims 9-15 correspond to claims 16-22, respectively, amended as explained below. Claim 16 is limited to the "recombinant cytokine" of claim 9. Claim 17 is limited to the "recombinant cytokine SEQ ID NO: 6" of claim 9. Independent claim 18 is directed to an "N-terminally truncated fragment" of the claimed cytokine. Claim 19 is limited to the (claim 18) N-terminally truncated fragment of either residues 8-74 of recombinant SEQ ID NO: 6 or residues 9-74 of recombinant SEQ ID NO: 6.

Present claim 12 corresponds to parent application claim 18 rewritten as an independent claim – "cDNA fragment SEQ ID NO: 7." Present claims 14 and 15 are limited to the invention elected in the parent application – the subject matter in parent application claims 21 and 22 relating to antibodies directed against the cytokine is not recited in the present claims.

In order to satisfy the utility requirement of 35 USC 101, applicants present the following comparisons between the presently claimed SEQ ID NO: 6 protein (HCC-1) and each of known inflammatory cytokines (1) CCL-3, also known as macrophage inflammatory protein (MIP) 1α, (2) CCL-4, also known as MIP-1β, and (3) CCL18 (DC-CK 1). The presentation shows there is significant analogy/homology between HCC-1 and the known inflammatory cytokines.

1) HCC-1 and MIP-1α are (a) identical in 35 out of 68 amino acids – an identity of 51% – and (b) homologous in 52 out of 68 amino acids – a homology of 76%.

```
HCC-1 / MIP-1a
Identities = 35/68 (51%), Positives = 52/68 (76%)

HCC-1    20 TKTESSSRGPYHPSECCFTYTTYKIPRQRIMDYYETNSQCSKPGIVFITKRGHSVCTNPSDKWVQDYIKDMKEN   93
                S+S      P+ CCF+YT+ +IP+  I DY+ET+SQCSKPG++F+TKR   VC +PS++WVQ Y+ D++
MIP-1α   22      SASLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPGVIFLTKRSRQVCADPSEEWVQKYVSDLElSA   92
```

2) HCC-1 shares 35 out of 70 amino acids with MIP-1β. An identity of 50% exists between these two proteins. The homology is even higher, with 50 out of 70 amino acids being homologous – a homology of 71%.

```
HCC-1 / MIP-1b
Identities = 35/70 (50%), Positives = 50/70 (71%)

HCC-1    20  TKTESSSRGPYHPSECCFTYTTYKIPRQRIMDYYETNSQCSKPGIVFITKRGHSVCTNPSDKWVQDYIKDMKEN  93
                S+  G   P+ CCF+YT  K+PR  ++DYYET+S CS+P +VF TKR   VC +PS+ WVQ+Y+ D++ N
MIP-1β   23      SAPMGSDPPTACCFSYTARKLPRNFVVDYYETSSLCSQPAVVFQTKRSKQVCADPSESWVQEYVYDLELN  92
```

3) A further sufficiently analogous cytokine is CCL18, with which HCC-1 shares 31 out of 59 amino acids, i.e., an identity of 52% exists. The homology is even higher with 45 out of 59 amino acids being homologous, i.e., a homology of 76% exists.

```
HCC-1 / CCL18
Identities = 31/59 (52%), Positives = 45/59 (76%

HCC-1   20  TKTESSSRGPYHPSECCFTYTTYKIPRQRIMDYYETNSQCSKPGIVFITKRGHSVCTNPSDKWVQDYIKDMKEN   93
                      CC  YT+++IP++ I+DY ET+ QC KPG++ +TKRG  +C +P+ KWVQ YI D+K N
CCL18   21         AQVGTNKECCLVYTSWQIPQKFIVDYSETSPQCPKPGVILLTKRGRQICADPNKKWVQKYISDLKLNA  89
```

All three foregoing analogs of HCC-1 exhibit clinical efficacy in treating a specific pathological condition.

For example CCl-3 (MIP-1α) is known to be an immune modulator, with potential for fighting bacterial infection. The attached abstract of *Infect. Immun. 71*, 2003, 1306-15 (Zeng et al.) teaches that MIP-1α (CCL3) is an important mediator of leukocyte recruitment and activation in a variety of inflammatory states, including infection. The findings by these authors stress the importance of MIP-1α for inducing cell immigration of selected leukocyte populations in vivo. They identify this cytokine as a potential immunoadjuvant to be employed in the setting of localized bacterial infection. Thus a technical expert interested in employing the cell immigration inducing activity of HCC-1, as it was claimed in the originally submitted set of claims (claim 7), would apply the teachings of Zeng et al.

The attached abstract of *J. Leukoc Biol., 72*, 2002, 1190-7 (Takahashi et al.) evidences that CCL-3 (MIP-1α) is essential for function of the immune system – of enabling it to fight off bacterial sepsis. The reference shows that macrophages are the major immune effector cells responsive to CCL-3, suggesting the use for CCL-3 in diseases of the immune system, e.g., in order to boost the ability of the immune system to fight sepsis. In the originally submitted claims, the use of HCC-1 was claimed for diseases of the immune system.

Further evidence of the usefulness of CCL-3 (MIP-1α) is provided by the attached abstract of *Nature, 344*, 1990, 442-4 (Graham et al). The document shows that CCL-3 can be prophylactically used to minimize the damage to haematopoietic stem cells during chemotherapy.

MIP-1α and MIP 1-β also have potential as AIDS therapeutics, as the attached abstract by Cocchi et al. (*Science, 270*, 1995 1811-5) – commented on by Mackewicz et al. (*Science, 274*, 1996

1393-5), summary page attached – teaches. MIP-1α and MIP-1β are identified in the reference as the major HIV suppressive factors produced by CD8+ T-cells. Cocchi et al. also suggest that these cytokines may have relevance for the prevention and treatment of AIDS. AIDS essentially is a disease of the immune system. Thus, the teachings of Cocchi et al. would help to enable one skilled in the art to apply the teachings of the present application and, so, use HCC-1 to treat diseases of the immune system.

The cytokine CL18, which is also a homolog of HCC-1, is an immuno-modulator having therapeutic potential against malaria and other diseases where the cellular immune response is crucial. The attached abstract by Bruna-Romero et al. (*J. Immunol., 170*, 2003 3195-203) shows that CCL18 (DC-CK1) has a crucial role in the establishment of primary T-cell responses, and it indicates that this chemokine has potential as an adjuvant for administration with vaccines against malaria and other diseases in which cellular immune responses are important. One skilled in the art would also deduce from Bruna-Romero et al. the potential of CCL 18 to strengthen the primary T-cell response of a diseased immune system. Accordingly, by analogy, the cytokine of the present claims is useful for strengthening a diseased immune system.

Finally, the attached abstract by Hogaboam et al. (*Curr. Pharm Des. 6*, 2000, 651-63) provides a review of the therapeutic applications of chemokines. Hogaboam et al. discusses chemokines involved in a number of pathological processes and why chemokines represent important targets. This review highlights novel therapies that use chemokines, including viral-encoded chemokines, recombinant chemokines, and genetically engineered chemokines, to treat a

number of diseases and disorders. Advances in the application of novel chemokine delivery procedures – both at the research level and the clinical level – are also discussed in the reference. Overall, this review teaches the utilization of chemokines to prevent and treat disease and their tremendous potential, which certainly also extends to HCC-1 of the present claims.

Claims in the parent application were subject to final rejection under 35 USC 102(e) as allegedly anticipated by US5556767 (Rosen) and under 35 USC 103(a) as allegedly unpatentable based on Rosen combined with US5858688 (Haskill), US4438032 (Golde), US4230697 (Nishida), and US4569790 (Koths). Neither Rosen, nor Rosen combined with Haskill, Golde, Nishida, and Koths, teaches or suggests any of the present claims.

Rosen discloses a polypeptide that is 93 amino acids long (Rosen, Fig. 1 and SEQ ID NO: 2). This 93-amino-acid polypeptide neither teaches nor suggests the 74-amino-acid cytokine of the present claims – SEQ ID NO: 6 in the present "Sequence Listing" – or the "N-terminally truncated fragment," thereof, of the present claims.

Additionally, Rosen teaches that this 93-amino-acid polypeptide is a protein precursor of the protein identified "MIP-1γ" by the reference. According to Rosen, "MIP-1γ" is 69 amino acids long – amino acids 1_{Ser}-69_{Asn} of Rosen SEQ ID NO: 2. The 69-amino-acid "MIP-1γ" of Rosen corresponds to residues 6-74 of SEQ ID NO: 6 – which is excluded from the N-terminally truncated fragment presently claimed.

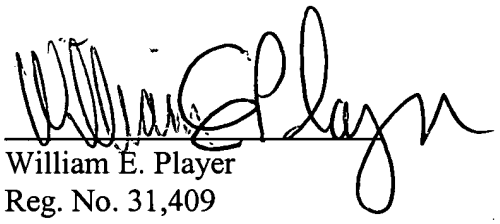
Therefore, neither the "SEQ ID NO: 2" nor the "MIP-1γ" disclosed in Rosen teaches or suggests any of the present claims. Moreover, none of the aforesaid secondary references, taken

alone or in combination, makes up for this fatal flaw in Rosen as the primary reference relied on in the rejection under §103(a). Accordingly, neither the final §102(e) nor the final §103(a) rejection of the parent application would be applicable against any of the present claims.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: January 11, 2005
WEP/bad
R:\rthomas\2005\January\P60448US1-preamd.wpd

1: Infect Immun. 2003 Mar;71(3):1306-15. Related Articles,

Full text article at iai.asm.org

Intrapulmonary expression of macrophage inflammatory protein 1alpha (CCL3) induces neutrophil and NK cell accumulation and stimulates innate immunity in murine bacterial pneumonia.

Zeng X, Moore TA, Newstead MW, Hernandez-Alcoceba R, Tsai WC Standiford TJ.

Department of Medicine, Division of Pulmonary and Critical Care Medic The University of Michigan Medical School, Ann Arbor, Michigan 4810 0360, USA.

Macrophage inflammatory protein 1alpha (MIP-1alpha) (CCL3) is an important mediator of leukocyte recruitment and activation in a variety of inflammatory states, including infection. A recombinant human type 5 adenovirus containing the murine MIP-1alpha cDNA (AdMIP-1alpha) wa constructed to determine the effect of transient intrapulmonary expressior MIP-1alpha on leukocyte recruitment, activation, and bacterial clearance murine model of Klebsiella pneumoniae pneumonia. The intratracheal administration of AdMIP-1alpha resulted in both time- and dose-depende expression of MIP-1alpha mRNA and protein within the lung. Importantl the intrapulmonary overexpression of MIP-1alpha resulted in a maximal and 100-fold reduction in lung and blood bacterial burden, respectively, i animals cochallenged with K. pneumoniae, which was associated with a significant increase in neutrophil and activated NK cell accumulation. Furthermore, the transgenic expression of MIP-1alpha during bacterial pneumonia resulted in enhanced expression of gamma interferon mRNA, compared to that observed in Klebsiella-challenged animals pretreated wi control vector. These findings indicate an important role for MIP-1alpha the recruitment and activation of selected leukocyte populations in vivo a identify this cytokine as a potential immunoadjuvant to be employed in th setting of localized bacterial infection.

PMID: 12595446 [PubMed - indexed for MEDLINE]

1: J Immunol. 2003 Mar 15;170(6):3195-203. Related Articles,

Full text article at www.jimmunol.org

The dendritic cell-specific chemokine, dendritic cell-derived C chemokine 1, enhances protective cell-mediated immunity to murine malaria.

Bruna-Romero O, Schmieg J, Del Val M, Buschle M, Tsuji M.

Department of Medical and Molecular Parasitology, New York Universit School of Medicine, New York, NY 10010, USA.

Cell-mediated immunity plays a crucial role in the control of many infect diseases, necessitating the need for adjuvants that can augment cellular immune responses elicited by vaccines. It is well established that protecti against one such disease, malaria, requires strong CD8(+) T cell response targeted against the liver stages of the causative agent, Plasmodium spp. I this report we show that the dendritic cell-specific chemokine, dendritic c derived CC chemokine 1 (DC-CK1), which is produced in humans and ac on naive lymphocytes, can enhance Ag-specific CD8(+) T cell responses when coadministered with either irradiated Plasmodium yoelii sporozoite a recombinant adenovirus expressing the P. yoelii circumsporozoite prote mice. We further show that these enhanced T cell responses result in increased protection to malaria in immunized mice challenged with live F yoelii sporozoites, revealing an adjuvant activity for DC-CK1. DC-CK1 appears to act preferentially on naive mouse lymphocytes, and its adjuvar effect requires IL-12, but not IFN-gamma or CD40. Overall, our results s for the first time an in vivo role for DC-CK1 in the establishment of prim T cell responses and indicate the potential of this chemokine as an adjuva for vaccines against malaria as well as other diseases in which cellular immune responses are important.

PMID: 12626578 [PubMed - indexed for MEDLINE]

1: Nature. 1990 Mar 29;344(6265):442-4. Related Articles,

Identification and characterization of an inhibitor of haemopoietic stem cell proliferation.

Graham GJ, Wright EG, Hewick R, Wolpe SD, Wilkie NM, Donalds D, Lorimore S, Pragnell IB.

Beatson Institute for Cancer Research, Glasgow, UK.

The haemopoietic system has three main compartments: multi-potential s cells, intermediate stage progenitor cells and mature cells. The availabilit simple reproducible culture systems has made possible the characterizatic and purification of regulators of the progenitor cells, including colony-stimulating factors and interleukins. In contrast, our knowledge of the regulators involved in the control of stem cell proliferation is limited. The steady-state quiescent status of the haemopoietic stem cell compartment i thought to be controlled by locally acting regulatory elements present in t stromal microenvironment, but their purification has been hampered by tl lack of suitable culture systems. We have recently developed a novel in v colony assay that detects a primitive cell (CFU-A) which has similar proliferative characteristics, in normal and regenerating bone marrow, to CFU-S (haemopoietic stem cells, as defined by the spleen colony assay) a which responds to CFU-S-specific proliferation regulators. We have now used this assay to purify to homogeneity a macrophage-derived reversible inhibitor of haemopoietic stem cell proliferation (stem cell inhibitor, SCI) Antibody inhibition and sequence data indicate that SCI is identical to a previously described cytokine, macrophage inflammatory protein-1 alpha (MIP-1 alpha), and that SCI/MIP-1 alpha is functionally and antigenically identical to the CFU-S inhibitory activity obtained from primary cultures normal bone marrow cells. The biological activities of SCI/MIP-1 alpha suggest that it is a primary negative regulator of stem cell proliferation an that it has important therapeutic applications in protecting haemopoietic s cells from damage during cytotoxic therapies for cancer.

PMID: 2320111 [PubMed - indexed for MEDLINE]

1: Curr Pharm Des. 2000 Apr;6(6):651-63. Related Articles,

Therapeutic use of chemokines.

Hogaboam CM, Bone-Larson C, Matsukawa A, Steinhauser ML, Ble K, Lukacs NW, Kunkel SL.

Department of Pathology, University of Michigan Medical School, Ann Arbor, MI 48109, USA. hogaboam@path.med.umich.edu

Chemokines are involved in a number of pathological processes, and therefore represent important targets. However, it has also become appare that chemokines have exciting therapeutic applications in inflammatory, infectious and cancer-related diseases. The following review will highligl the application of novel therapies including viral-encoded, recombinant, a genetically engineered chemokines to a number of diseases or disorders. Advances in the application of novel chemokine delivery procedures both the research bench and the clinical bedside will also be discussed. Overal utilization of chemokines to prevent and treat disease has tremendous potential.

Publication Types:
- Review
- Review, Academic

PMID: 10788602 [PubMed - indexed for MEDLINE]

1: Science. 1995 Dec 15;270(5243):1811-5. Related Articles,

Comment in:
- Science. 1996 Nov 22;274(5291):1393-5.

Identification of RANTES, MIP-1 alpha, and MIP-1 beta as t major HIV-suppressive factors produced by CD8+ T cells.

Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P

Laboratory of Tumor Cell Biology, National Cancer Institute, Bethesda, I 20892, USA.

Evidence suggests that CD8+ T lymphocytes are involved in the control c human immunodeficiency virus (HIV) infection in vivo, either by cytolyt mechanisms or by the release of HIV-suppressive factors (HIV-SF). The chemokines RANTES, MIP-1 alpha, and MIP-1 beta were identified as th major HIV-SF produced by CD8+ T cells. Two active proteins purified fi the culture supernatant of an immortalized CD8+ T cell clone revealed sequence identity with human RANTES and MIP-1 alpha. RANTES, MI alpha, and MIP-1 beta were released by both immortalized and primary CD8+ T cells. HIV-SF activity produced by these cells was completely blocked by a combination of neutralizing antibodies against RANTES, M alpha, and MIP-1 beta. Recombinant human RANTES, MIP-1 alpha, and MIP-1 beta induced a dose-dependent inhibition of different strains of HI HIV-2, and simian immunodeficiency virus (SIV). These data may have relevance for the prevention and therapy of AIDS.

PMID: 8525373 [PubMed - indexed for MEDLINE]

1: Science. 1996 Nov 22;274(5291):1393-5. Related Articles,

Comment on:
- Science. 1995 Dec 15;270(5243):1811-5.

Full text article at www.sciencemag.org

Role of beta-chemokines in suppressing HIV replication.

Mackewicz CE, Barker E, Levy JA.

Publication Types:
- Comment
- Letter

PMID: 8966605 [PubMed - indexed for MEDLINE]